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PATENT
Attorney Docket No. 15280-169300

On 4-9-02

TOWNSEND and TOWNSEND and CREW LLP

By: Linda Shaffer



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In re application of:

Louis E. Henderson, *et al.*

Application No.: 09/431,607

Filed: November 1, 1999

For: METHOD FOR IDENTIFYING
AND USING COMPOUNDS THAT
INACTIVATE HIV-1 AND OTHER
RETROVIRUSES BY ATTACKING
HIGHLY CONSERVED ZINC FINGERS
IN THE VIRAL NUCLEOCAPSID
PROTEIN

Examiner: S. Foley

Art Unit: 1648

REQUEST FOR RECONSIDERATION

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Request for Reconsideration is submitted in response to the Office Action mailed October 2, 2001. A Petition for a three-month extension of time is submitted concurrently herewith in a separate paper to extend the time for response to on or before April 2, 2002. Applicants respectfully request reconsideration and further examination of the above-referenced patent application in view of the amendments and remarks presented herein.

The Invention

The present invention provides compositions comprising inactivated retrovirus, wherein the retrovirus is inactivated by contact with a compound selected from several classes of compounds which can be used to inactivate retroviruses by attacking the CCHC zinc fingers of the viral nucleocapsid protein and ejecting the zinc therefrom. These compositions comprising inactivated retrovirus can be used, for example, as vaccines, as prophylactics, or as components in standard ELISA assays for the diagnosis of retroviral infections.

Status of the Claims

Claims 22-27 are pending in the above-referenced application and are currently under examination.

The claims were rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. The claims were further rejected under 35 U.S.C. § 112, first paragraph, for alleged new matter and alleged lack of written description. Claims 22-24, 26 and 27 were rejected for alleged anticipation by Ryser *et al.*, *PNAS*, 91:4559-4563 (1994) ("Ryser, *et al.*"). In addition, the claims were rejected for alleged anticipation by PCT Application No. WO 94/19321 ("Williams, *et al.*"). Claims 22-24, 26 and 27 were also rejected for alleged anticipation by PCT Application No. WO 93/15730 ("Levine, *et al.*"). Claims 22, 26 and 27 were rejected for alleged anticipation by Rice, *et al.*, *Nature*, 361:473-473 (1993) ("Rice *et al.*"). Claims 22, 26 and 27 were rejected for alleged anticipation by PCT Application No. WO 92/15329 (Levine, *et al.*). For the reasons set forth herein, each of the Examiner's rejections is overcome.

Rejection Under 35 USC § 112, Second Paragraph

Claims 22-27 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claim 22 is drawn to a composition comprising an inactivated retrovirus that has been inactivated by a compound selected from several classes of

compounds which can be used to inactivate retroviruses by attacking the CCHC zinc fingers of the viral nucleocapsid protein and ejecting the zinc therefrom. These compounds include nitric oxide and derivatives containing the NO group, cupric ions and complexes containing Cu^{+2} , and ferric ions and complexes containing Fe^{+3} . The Office Action alleges that it is not clear what a "derivative of a substance containing an NO group" is defined as. In addition, the Office Action alleges that substances containing cupric ions or ferric ions and "complexes" have not been defined in a manner that can be readily interpreted. Applicants disagree, and respectfully traverse the rejection.

The phrase "nitric oxide and derivatives containing the NO group" in claim 22 clearly refers to nitric oxide and molecules that contain a nitric oxide group. One of skill in the art would recognize molecules that contain a nitric oxide group, as they are apparent by the presence of a NO group in the chemical formula of the derivative containing the NO group. According to the specification, a study of the reaction mechanism of NC zinc displacement, present for the first time in the present application, reveals that CCHC zinc finger arrays act as selective electron donors and, thus, are capable of donating electrons to suitable electron acceptors (*see*, page 19, lines 2-5 of the specification). One of skill in the art knows that nitric oxide and derivatives containing the NO group are suitable electron acceptors, and it is reasonable to expect, based on the information provide by the present disclosure, that these compounds may be used to dissociate a zinc ion from a CCHC zinc finger of a retroviral nucleocapsid protein, which thereby inactivates the retrovirus (*see*, page 19, in lines 20-21 of the specification). Thus, a "derivative containing an NO group" is clearly defined by the specification as a molecule containing an NO group which accepts electrons from the CCHC finger (*see*, page 19, lines 5-10 of the specification). In addition, the specification provides *in vitro* assays that can be used to easily screen these derivatives for compounds that have the ability to inactivate retroviruses by attacking the CCHC zinc fingers of the viral nucleocapsid protein and ejecting the zinc therefrom (*see*, pages 11-17 of the

specification). Thus, Applicants respectfully request that the rejection under U.S.C. § 112, second paragraph, be withdrawn.

Complexes containing Cu^{+2} or Fe^{+3} are readily recognized by one of skill in the art as a molecules, or a group of molecules, that contain cupric or ferric ions, respectively. Complexes that contain Cu^{+2} or Fe^{+3} accept electrons from the CCHC fingers, and, therefore, may be used to dissociate a zinc ion from a CCHC zinc finger of a retroviral nucleocapsid protein, which thereby inactivates the retrovirus. The specification discloses many compounds with the ability to inactivate retroviruses in the described manner, including, for example, cupric chloride (*see*, page 24, lines 6-12 of the specification). Furthermore, the specification describes a set of specific tests and reagents that can be used to screen and identify compounds based on their ability to react with and disrupt retroviral zinc fingers in the viral NC proteins (*see*, page 3, lines 21-24 of the specification). Thus, complexes containing Cu^{+2} or Fe^{+3} are clearly defined and recognizable by one of skill in the art. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph

A. New Matter Rejection

Claim 22 was rejected as allegedly containing new matter. According to the Office Action, the specification does not contain support for the negative limitation of claim 22, which states that the compound that inactivates the retrovirus is not a C-nitroso compound having the formula R-C-NO . Applicants respectfully traverse the rejection.

It was known in the art at the time of the invention that a C-nitroso compound having the formula: R-C-NO may be used for retroviral inactivation (*see*, Rice *et al.*). However, Rice, *et al.* do *not* teach or suggest the use of C-nitroso compounds for zinc dissociation for CCHC zinc fingers. Since the mechanism used by C-nitroso compounds to inactivate retrovirus was not known prior to the present invention, it would not have been obvious to one of skill in the art that unrelated suitable

electron acceptors may be used to dissociate a zinc ion from a CCHC zinc finger of a retroviral nucleocapsid protein, thereby inactivating the retrovirus. Thus, compounds not related to R-C-NO would not have been expected to inactivate retrovirus prior to the time of the present invention.

To make it as explicit as possible that the present claims are not directed to the use of C-nitroso compounds for retroviral inactivation as taught by Rice, *et al.*, the claims include the express limitation that the compound used for retroviral inactivation is "not a C-nitroso compound of the formula R-C-NO". Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Written Description Rejection

Claims 22-27 were rejected under U.S.C. 112, first paragraph, for alleged lack of written description. The Office Action alleges that there is no written description that identifies a range of structures to enable any compound containing cupric ions or ferric ions or NO derivatives that would immediately identify itself to one of skill in the art to practice the invention. Applicants respectfully traverse the rejection.

The present invention relates to several classes of compounds which can be used to inactivate retroviruses by attacking the CCHC zinc fingers of the viral nucleocapsid protein and ejecting the zinc therefrom (*see*, Abstract of the specification). The specification discloses the discovery of the mechanism by which the CCHC zinc fingers of retroviral nucleocapsid proteins are disrupted (*see*, page 2, lines 27-28 of the specification). This mechanism provides investigators with a means of predicting which compounds can effectively disrupt the CCHC zinc fingers, and, in turn, inactivate the retrovirus of interest.

The mechanism by which CCHC zinc fingers are disrupted by a nitroso reagent is set forth in Figure 3 of the specification. In the first stage, thiolates in each of the two zinc fingers of the NC protein of HIV-1, for example, donate electrons to form a disulfide with the elimination of zinc. This requires two electrons and can proceed via

adducts in successive single-electron steps, or, alternatively, via a two-electron transfer to hydroxylaminobenzamide directly (*see*, page 3, lines 3-8 of the specification).

Based upon the foregoing, several classes of compounds have now been discovered which can be used to inactivate retroviruses by attacking the CCHC zinc fingers and ejecting the zinc therefrom (*see*, page 3, lines 18-20 of the specification). The specification discloses many compounds with the ability to inactivate retroviruses in the described manner, including, for example, tetraethylthiuram disulfide (*see*, page 22, lines 25-26), and cupric chloride (*see*, page 24, lines 6-12 of the specification). A number of compounds suitable for testing for their ability to inactivate retrovirus using the methods disclosed in the specification are found in Table 2, on pages 31-33 of the specification.

The specification describes a set of specific tests and reagents that can be used to screen and identify compounds based on their ability to react with and disrupt retroviral zinc fingers in the viral NC proteins (*see*, page 3, lines 21-24 of the specification). Such tests and reagents that can be used to screen include, for example, capillary zone electrophoresis, monitoring release of radioactive zinc from zinc-65 labeled p7NC, monitoring release of radioactive zinc from zinc-65 labeled whole virus, detection of disulfide cross-linked NC protein by gel-mobility shift assays, high pressure liquid chromatography purified NC protein for structural characterization of reaction products, and nuclear magnetic resonance-based detection of zinc loss from retroviral NC proteins (*see*, pages 11-17 of the specification).

As set forth in the attached expert declaration¹ by Dr. Rice, "it is well accepted in the art that retroviral nucleocapsid proteins universally and specifically bind zinc." (*See*, the attached declaration of Dr. Rice at page 3, first full paragraph.) Moreover, Dr. Rice has provided a number of references which unequivocally establish that there is conservation of both structure and function for CCHC zinc fingers for all retroviruses. For instance, Dr. Rice submits Bess, *et al.*, *The Journal of Virology* 60:840-

847 (1992) as Exhibit 3 with his declaration, providing additional objective evidence that the conservation of the zinc finger structure in retroviruses correlates with zinc binding. Bess *et al.* demonstrate that zinc is tightly bound to HIV-1, SIV, EAIV, BLV, Mo-MuLV, MMTV, MPMV AND H9 mock virus. Bess, *et al.* thus demonstrate the conservation of zinc finger nucleocapsid structure and zinc-binding function among both the Lentiviruses and Oncoviruses. In light of Bess, *et al.* and the declaration submitted by Dr. Rice, it is clear that there is conservation of both structure and function for CCHC zinc fingers by all retroviruses which comprise a CCHC zinc finger motif in their respective nucleocapsid protein.

Moreover, to unequivocally prove that the methods of the invention are generally applicable to inactivation of retroviruses other than HIV, Dr. Rice provides Rein, *et al.*, *The Journal of Virology* 70(8):4966-4972 (1996), of which he is an author, as Exhibit 5 with his declaration. Rein *et al.* demonstrate that the methods of the invention are applicable to retroviruses other than HIV, by showing that disulfides such as disulfide-substituted DIBA-2, DPMTD, aldrithiol, and tetraethylthiuram disulfide all inactivate MuLv (an oncoretrovirus). *See, e.g.*, page 4790 of Rein, *et al.* However, a Fomey virus (a spumaretrovirus which lacks the CCHC zinc finger motif) is unaffected by disulfide compounds. Rein, *et al.* also note that all retroviral nucleocapsid proteins except the spumaretroviruses have CCHC nucleocapsid protein zinc fingers. (*See, the abstract.*)

As stated by Dr. Rice, in light of evidence available to one of skill in the art at the time of filing and in light of the subject application, one of skill would understand that disulfides, maleimides, α -halogenated ketones, hydrazides, nitric oxide and derivatives, cupric ions and ferric ions can be used to inactivate any retrovirus which has a CCHC zinc finger in the nucleocapsid proteins. All retroviruses except the

¹ Originally submitted in response to the Office Action sent by the Patent Office on March 6, 1996, regarding U.S. Application No. 08/379,420, filed January 27 1995. A copy is attached herewith for the convenience of the Examiner.

spumaretroviruses have CCHC nucleocapsid protein zinc fingers, and the CCHC zinc fingers are both structurally and functionally conserved.

Because of the highly conserved nature of the retroviral nucleocapsid protein CCHC zinc fingers, one of skill would expect that compounds which inactivate a zinc finger in one retrovirus are highly likely to inactivate the CCHC zinc finger in all other CCHC zinc finger retroviruses. In the present case, the effects of the methods of the invention have been shown to be conserved from the lentiviruses (*e.g.*, HIV) to the oncoviruses (*e.g.*, MuLv). The fact that both lentiviruses and oncoviruses behave in the same manner with regard to the methods of the invention make it clear that the structure and function of the CCHC zinc fingers is evolutionarily very well conserved, and that the methods described in the specification are broadly applicable to all retroviral CCHC zinc fingers.

Based upon the foregoing, it is clear that the specification clearly provides sufficient written description to enable one of skill in the art to practice the invention. The specification discloses classes of compounds that may inactivate retroviruses, provides several examples of such compounds, and discloses methods of screening these compounds for their ability to inactivate retroviruses. Accordingly, Applicants respectfully request that the rejection of the claims be withdrawn.

Rejection under 35 USC § 102(a)

1. Rejection under 35 USC § 102(a) in view of Ryser *et al.*

Claims 22-24, 26, and 27 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Ryser, *et al.* The Office Action alleges that the abstract of Ryser, *et al.*, which discloses that HIV infection of human lymphoid cells is markedly inhibited by 5,5'-dithiobis(2-nitrobenzoic acid), by bacitracin, and by anti-PDI antibodies, anticipates claims 22-24, 26 and 27 of the present invention. Applicants respectfully traverse the rejection.

“To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.” *PPG Industries Inc. v. Guardian Industries Corp.*, 7 USPQ2d 1618, 1624 (Fed. Cir. 1996).

Ryser, *et al.* teach that inhibition of human immunodeficiency virus infection can be mediated by agents that interfere with thiol-disulfide interchange upon virus-receptor interaction (*see*, page 4559, second column, top paragraph). Ryser, *et al.* postulate that the plasma membrane of human lymphoid cells would have a reductive function, and that the reductive mechanism might cleave disulfides in membrane-bound gp120 and facilitate viral entry into cells (*see*, page 4559, first column, last sentence bridging to column 2). In contrast, claim 22 of the present invention is drawn to a composition comprising an *inactivated retrovirus*, wherein the retrovirus is inactivated by contact with a compound selected from a group of specified compounds defined in the specification and claim. As stated in the specification, and as readily apparent to one of skill in the art, inactivated retrovirus can be used, for example, as vaccines, as prophylactics, or as components in standard ELISA assays for the diagnosis of retroviral infections (*see*, page 11, lines 20-23 of the specification).

In contrast, Ryser, *et al.* teach the reduction of HIV infection, which is measured by assaying p24 viral protein in cell-free culture supernatants, *not* inactivated retrovirus (*see*, page 4560, column 1, “Measurement of HIV Infection”). Ryser, *et al.* are interested in the mechanism by which HIV enters mammalian cells, and disclose that HIV and its target cell may engage in a thiol-disulfide interchange mediated by PDI and that the reduction of critical disulfides in viral envelope glycoproteins may be the initial event that triggers conformational changes required for HIV entry and cell infection. Ryser *et al.* do not teach a composition comprising inactivated retrovirus, wherein the retrovirus is inactivated by contact with a compound, as recited in the pending claims. Therefore, Ryser, *et al.* do not anticipate the present invention, and Applicants respectfully request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

2. Rejection under 35 USC § 102(a) in view of Williams *et al.*

Claims 22-27 were rejected under 35 U.S.C. § 102(a) allegedly as being anticipated by Williams, *et al.* The Office Action alleges that Williams, *et al.* teach HIV inactivated by Bis (4-chlorophenyl) disulfide 2127-03-9. Applicants respectfully traverse the rejection.

As described above claim 22 of the present invention is drawn to a composition comprising an *inactivated retrovirus*, wherein the retrovirus is inactivated by contact with a compound selected from a group of specified compounds. In contrast, Williams, *et al.* teach novel indole compounds that inhibit the enzyme HIV reverse transcriptase. Williams, *et al.* disclose a number of compounds of a specific formula, and teach that these compounds are useful in the inhibition of HIV reverse transcriptase (see, page 2, lines 10-17, Williams, *et al.*). Moreover, Williams, *et al.* teach a reverse transcriptase assay to measure the incorporation of tritiated deoxyguanosine monophosphate by recombinant HIV reverse transcriptase in the presence or absence of various compounds (see, page 69, Williams, *et al.*). This assay utilizes purified HIV reverse transcriptase enzyme (see, page 69, lines 10-16, Williams, *et al.*). At no point do Williams, *et al.* teach a composition comprising an *inactivated retrovirus*, wherein the retrovirus is inactivated by contact with a compound as described by the specification. Applicants respectfully request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

3. Rejection under 35 USC § 102(a) in view of Levine, *et al.* (PCT Application No. WO 93/15730)

Claims 22-24, 26, and 27 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Levine, *et al.* (WO 93/15730). Applicants respectfully traverse the rejection.

Claim 22 of the present invention is drawn to a composition comprising an *inactivated retrovirus*, wherein the retrovirus is inactivated by contact with a compound selected from a group of specified compounds, which are defined by the specification and

in the claim. As stated in the specification, and as readily apparent to one of skill in the art, inactivated retrovirus can be used, for example, as vaccines, as prophylactics, or as components in standard ELISA assays for the diagnosis of retroviral infections (*see*, page 11, lines 20-23 of the specification).

In contrast, Levine, *et al.* teach a sulfhydryl-reactive compound, such as 5,5'-dithio-bis (2-nitrobenzoic acid). The claims of Levine, *et al.* are drawn to methods of inhibiting the growth or replication of a virus. Levine, *et al.* disclose that a sulfhydryl-reactive compound will react with the viral protease, thereby inhibiting the ability of the protease to cleave the viral polyprotein into its constituent proteins (*see*, pages 6, lines 24-31, bridging to lines 1-3 on page 7 of Levine *et al.*). Levine, *et al.* do **not** teach a composition comprising an inactivated retrovirus which can be used for vaccines, as a prophylactic, or as a component in assays for the diagnosis of retroviral infections. Therefore Levine *et al.* do not anticipate the present invention, and Applicants respectfully request that the rejection under 35 U.S.C. § 102(a) be withdrawn.

4. Rejection under 35 USC § 102(a) in view of Rice *et al.*

Claims 22, 26, and 27 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Rice, *et al.* The Office Action alleges Rice, *et al.* teach inactivation of HIV-1 with a C-nitroso compound. According to the Office Action, since support for the negative limitation in claim 22 could not be found in the original specification, and the C-nitroso compound would be a derivative of nitric oxide, Rice, *et al.* anticipates claims 22, 26, and 27. Applicants respectfully traverse the rejection.

For the reason presented above in section A., *i.e.*, it was known in the art at the time of the invention that a C-nitroso compound having the formula: R-C-NO may be used for retroviral inactivation (*see*, Rice, *et al.*). However, Rice, *et al.* do **not** teach or suggest the use of C-nitroso compounds for zinc dissociation for CCHC zinc fingers.

Dr. Rice, the primary author on the Rice *et al.* paper cited by the Office Action as allegedly anticipating the present invention, states in his Declaration that “the

paper does not disclose a mechanism for CCHC zinc finger inactivation by C-nitroso compounds..." One of skill in the art would not extrapolate from the inactivation of CCHC zinc fingers by C-nitroso compounds, as described in the paper, to the inactivation of CCHC zinc fingers by other classes of compounds, as taught in the present invention.

Dr. Rice cites objective reasons why one of skill would not have had a reasonable expectation that structurally unrelated compounds would work in the same manner as C-nitroso compounds. First as stated by Dr. Rice, because structurally unrelated compounds have different redox potentials, oxidation by C-nitroso compounds is not necessarily a model for oxidation by structurally unrelated compounds. Second, structurally unrelated compounds could have been unable to interact with CCHC zinc fingers due to steric interaction of the compounds the nucleocapsid protein and/or the solvent. Third, structurally unrelated compounds could have interacted with sites other than the CCHC zinc fingers on the nucleocapsid proteins, or other viral proteins, preventing the interaction with the CCHC zinc fingers. As stated by Dr. Rice, in the absence of the evidence presented in the subject application, which clearly shows that a wide variety of structurally unrelated compounds can be used to inactivate retroviral nucleocapsid proteins, there was no way of knowing whether the problems outlined above would prevent the use of structurally unrelated compounds for retroviral inactivation. Therefore, Rice *et al.* do not anticipate the present invention, and Applicants respectfully request that the rejection be withdrawn.

Rejection under 35 USC § 102(b)

Claims 22, 26, and 27 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Levine, *et al.* (WO 92/15329). Applicants respectfully traverse the rejection.

The present invention relates to a composition comprising an *inactivated retrovirus*, wherein the retrovirus is inactivated by contact with a compound selected from a group of specified compounds that are defined in the specification. As stated in

the specification, and as readily apparent to one of skill in the art, inactivated retrovirus can be used, for example, as vaccines, as prophylactics, or as components in standard ELISA assays for the diagnosis of retroviral infections (*see*, page 11, lines 20-23 of the specification).

Levine, *et al.* disclose that the aspartyl protease encoded by HIV-1 is essential for the processing of the viral polyproteins encoded by the *gag* and *pol* genes into mature viral proteins, and that mutation or deletion of the protease gene blocks replication of the virus, making the protease an attractive target for antiviral therapy of the acquired immunodeficiency syndrome. Levine, *et al.* teach an approach to the inhibition of the protease by using enzymatic and non-enzymatic metal-catalyzed oxidation systems to oxidatively inactivate the protease (*see*, page 1, lines 24-30, Levine, *et al.*). Levine, *et al.* do not teach a composition comprising inactivated retrovirus, nor do Levine, *et al.* suggest that such compositions may be used as vaccines, prophylactics, or as components in standard ELISA assays for the diagnosis of retroviral infections. Therefore, Levine, *et al.* do not anticipate the present invention. Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

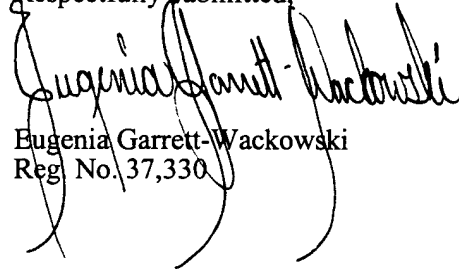
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Eugenia Garrett-Wackowski". The signature is fluid and cursive, with the first name "Eugenia" being the most prominent part.

Eugenia Garrett-Wackowski
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